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Peripheral Electrical Stimulation in Alzheimer's Disease

A Randomized Controlled Trial on Cognition and Behavior

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Key Words
Alzheimer's disease · Dementia · Transcutaneous electrical nerve stimulation

Abstract
In a number of studies, peripheral electrical nerve stimulation has been applied to Alzheimer's disease (AD) patients who lived in a nursing home. Improvements were observed in memory, verbal fluency, affective behavior, activities of daily living and on the rest-activity rhythm and pupillary light reflex. The aim of the present, randomized, placebo-controlled, parallel-group clinical trial was to examine the effects of electrical stimulation on cognition and behavior in AD patients who still live at home. Repeated measures analyses of variance revealed no effects of the intervention in the verum group (n = 32) compared with the placebo group (n = 30) on any of the cognitive and behavioral outcome measures. However, the majority of the patients and the caregivers evaluated the treatment procedure positively, and applying the daily treatment at home caused minimal burden. The lack of treatment effects calls for reconsideration of electrical stimulation as a symptomatic treatment in AD.

Introduction

Dysfunction of the cholinergic neurotransmitter system is one of the characteristics of Alzheimer's disease (AD) [1]. Early studies considered cell death in the nucleus basalis of Meynert (NBM) to be the cause of the diminished level of acetylcholine (ACh) [2, 3]. However, only a small proportion of cells in the NBM is actually lost in AD [4], and the observed lowered number of cholinergic markers is due to NBM atrophy rather than cell loss [5]. Swaab argued that therapeutic strategies in AD could be directed towards stimulation of neurons to improve metabolism and possibly reactivate impaired neurons in, e.g. the NBM [5–7]. Accordingly, improved functioning might be established by stimulating the central nervous system exogenously with, e.g. enriched environment.

In enriched environments, the organism is typically subject to multisensory input [8]. Unisensory stimulation techniques, such as bright light (visual sensory system) and tactile stimulation (somatosensory system) have yielded positive effects on several brain functions in mild cognitively impaired and demented patients [9]. Walking, another type of somatosensory stimulation, resulted in an increased release of extracellular ACh in the hippocampus of rats [10]. Somatosensory stimulation by means of peripheral electrical stimulation applied to the skin of rats showed an increased activity of the hippocampus and an elevated release of ACh in the hypothalamus [11].

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Somatosensory stimulation through transcutaneous electrical nerve stimulation (TENS) has been applied to AD patients in a number of placebo-controlled experiments [12–17]. In those studies, a small electrical current was applied to the skin of the upper back of AD patients. After application of the electrical stimulus 5 days a week for a period of 6 weeks, improvements were found in memory, verbal fluency, affective behavior, activities of daily living (ADL) and the rest-activity rhythm [for a review, see 18]. A Japanese group replicated effects on cognition and found a positive effect on pupillary light reflex [19]. The latter is considered an indication that the cholinergic function has improved [20]. Despite these encouraging findings, the positive effects of electrical stimulation must be interpreted with caution because of the small sample sizes ranging from 6 [19] to 18 [14].

In the studies described above, the participating AD patients lived in a nursing home. The research question of the present study was whether peripheral electrical nerve stimulation would also demonstrate positive effects on cognition and behavior of patients who still live at home. This randomized, placebo-controlled, parallel-group clinical trial is unique since a family caregiver applied the treatment. Based on previous positive findings, it was hypothesized that after a treatment period of 6 weeks the verum group would show improved functioning in cognition and behavior compared with the control group.

Materials and Methods

Participants

Participants were recruited from the Alzheimer Center of the VU University Medical Center, the Department of Neurology, Sint Lucas Andreas Hospital and the community home care agency in Amsterdam, The Netherlands. Men and women were eligible if they had a diagnosis of probable AD according to the NINCDS/ADRDA criteria [21]. A Mini-Mental State Examination (MMSE) [22] score of 26 or lower and sufficient hearing and vision were required. In addition, it was essential that the AD patient was living at home with a partner or other family member who served as primary caregiver (the partner or other family member is further referred to as family caregiver). Patients with a diagnosis of dementia other than AD, cerebrovascular disease or clinical depression were excluded, as were patients who had a history of cerebral trauma, disturbances of consciousness, seizures, epilepsy or an infectious disease. Also, patients with a cardiac pacemaker were excluded because of reported interference between a pacemaker and an electrical stimulator [23].

After the procedure of the study had been fully explained, written informed consent was obtained from the patient and/or the family caregiver. The study was approved by the local medical ethical committees and by the committee on research involving human subjects in The Hague, The Netherlands.

Study Design

In this 12-week, randomized, placebo-controlled, parallel-group study, assessment of cognition and behavior took place at baseline (pre), after the treatment period of 6 weeks (post) and following a treatment-free period of 6 weeks (delayed). Additionally, a questionnaire covering applicability and efficacy of the treatment according to the patient and caregiver was administered after treatment.

Intervention

A standard commercially available TENS device (Premier 10s®, Xytron Medical, Apeldoorn, The Netherlands) was used. It produced biphasic square pulses with a width of 100 μs, applied in bursts of 9 pulses with a frequency of 160 Hz and a repetition rate of 2 Hz. Self-adhesive medical electrodes for electrical stimulation (XyTrode®, Xytron Medical) were placed on the back at the first thoracic vertebra, lateral to the spine. The intensity of the stimuli was set at a level that produced painless, visible muscular twitches. These stimulation parameters were chosen to optimally target afferent nerve fibers, i.e. A-Beta, A-Delta and C-fibers, which convey the pulses to subcortical and cortical areas [for more details, see 13]. The family caregiver applied the treatment for 30 min a day, 7 days a week, for a period of 6 weeks. To minimize interference in the daily routine of the participants, the patient and family caregiver were free to decide what time of the day they would administer the treatment.

Randomization and Blinding

Participants were allocated to either the verum or the placebo treatment using simple randomization by tossing an unbiased coin. Participants assigned to the verum group received verum treatment, whereas participants in the placebo group were told that the stimulator was working as soon as the green light was blinking without current being applied. To maintain the participants' blindness, and because they knew there was a verum and a placebo condition, the two groups were informed as follows. The verum group was told that different pulse frequencies were applied to both groups: one frequency that might have the desired effect and one that, on theoretical grounds, was unlikely to be effective. Hence, patients who received the verum treatment, felt the stimulus and the caregiver would observe muscle contraction, would still be under the assumption that they might be treated with noneffective stimuli. The participants in the placebo group were also told that we were applying different pulse frequencies in two groups, but that the pulse frequencies were in a range that could not be perceived. The neuropsychologist who instructed the participants about the use of the electrical stimulator (K.R.A.V.D), was not blinded to group allocation because a different instruction was required when explaining the use of the electrical stimulator to the verum and placebo groups. Patients, family caregivers and test administrators were blinded to group allocation.

Cognitive Measures

Digit Span, a subtest of the Wechsler Memory Scale [24], consists of a Forward and a Backward condition. The Forward condition served as a measure of attention for verbally presented stimuli and the Backward condition was used as a measure of working memory for verbally presented stimuli. The score for each condition is the number of correctly reproduced sequences.

Visual Memory Span [24] is the nonverbal equivalent of the Digit Span test. The Forward and the Backward condition served as a measure of attention and working memory for visually presented stimuli, respectively. The score for each condition is the number of correctly reproduced sequences.

The Eight Words Test of the Amsterdam Dementia Screening test [25] was used to assess verbal episodic memory. The immediate recall score is the total number of correct words after 5 trials and is used as a measure of the patients' ability to process and learn verbal stimuli. The delayed recall score is the total number of correctly reproduced words after a delay of approximately 10 min, measuring active retrieval of information from verbal memory. The recognition score is the total of correct responses minus incorrect responses, and measures recognition of the previously presented stimuli.

Face Recognition of the Rivermead Behavioural Memory test [26] was used as a measure of visual, nonverbal long-term recognition memory.

Picture Recognition of the Rivermead Behavioural Memory test [26] served as a measure of visual, verbal long-term recognition memory.

The Stroop Color Word test [27] was used to obtain a measure of interference control, i.e. the ability to disregard an automated response. The interference score is computed by subtracting the correctly named colors in 45 s on the color card from the correctly named colors in 45 s on the color/word card. A high interference score is an indication of poor interference control.

Category Fluency test was used to measure verbal fluency [28]. Categories were animals and professions. The total score for each category is the number of correct words produced in 60 s.

Self-Report Questionnaires Assessing Emotional Status

The patients reported the status of their emotional condition using the following questionnaires that were administered by an interviewer.

The Geriatric Depression Scale (GDS) [29], a Dutch 30-item version, was administered to assess symptoms of depression. Because the sample in the present study included cases of severe AD and because of known limited validity and reliability of the GDS when administered to cognitively impaired populations [30], a selection of 12 items was used to calculate the total score. The 12 selected items make up the GDS-12R, a screening measure appropriate for use with older people in nursing and residential care settings, including persons with cognitive impairment [31]. Internal reliability of the GDS-12R was 0.81 and 0.78 for those patients with an MMSE score below 10 [31].

The Philadelphia Geriatric Center Morale Scale (PGCMS) [32] was administered to obtain a measure of subjective well-being. This 17-item questionnaire is designed to measure dimensions of emotional adjustment in people aged 70–90. The total score on the 17 items is used as a measure of global life satisfaction.

Informant-Based Ratings of Functional and Emotional Status

The Philadelphia Geriatric Center Affect Rating Scale (PGCARS) [33] is an observation scale designed to rate affective states in dementia.

The Dutch Behavioral Observation Scale for Psychogeriatric Inpatients (GIP-28) [34] was used to assess psychiatric symptoms in 28 items. This shortened version is a modification of the original 82-item GIP [35] that is based on the Physical and Mental Impairment-of-Function Evaluation [36]. Three symptom dimensions were used as dependent variables: negative symptoms, cognitive symptoms and mood/affective symptoms [37].

ADL is a list of selected items obtained from Katz et al. [38] that are part of a larger patient-informant interview [39]. It was used as a measure of functional independence.

Applicability and Efficacy Questionnaire

In a questionnaire designed by the authors, applicability and efficacy of the treatment according to the patient and family caregiver were assessed. Part A consists of questions for the patient receiving the treatment and includes 2 subscales. (1) 'Perceived burden', ranging from 0 (no burden) to 12 (highest burden), and (2) 'Perceived efficacy', ranging from 0 (no benefit) to 4 (most benefit). Part B consists of items for the family caregiver and includes 4 subscales. (1) 'Difficulties using the apparatus' ranging from 0 (no burden) to 8 (highest burden); (2) 'Perceived burden for the family caregiver' ranging from 0 (no burden) to 8 (highest burden); (3) 'Perceived burden for the patient' ranging from 0 (no burden) to 12 (highest burden), and (4) 'Perceived efficacy' ranging from 0 (no benefit) to 4 (most benefit).

Statistical Analysis

Complete case method was used in which all patients with a missing response on an outcome variable were excluded from analysis regarding that variable. Comparisons of group characteristics were made using independent sample t tests for normally distributed data and Mann-Whitney U tests for categorical data. Dependent variables that were not normally distributed were transformed using square root or log transformation. For purpose of clarity, all means printed in the tables are the original values. To determine treatment effects, dependent variables were subject to repeated univariate analyses of variance (ANOVAs), employing transformed scores when applicable, with group (two levels: verum and placebo) as between subjects factor and time as within-subject factor (3 levels: pre, post and delayed). Treatment effects were hypothesized to emerge after the treatment period; therefore, post vs. pre contrasts were computed. To investigate if any effects lasted when the treatment was discontinued, delayed vs. pre contrasts were computed. Group differences on the applicability and efficacy questionnaire were analyzed using ANOVAs. To compensate for the use of multiple comparisons, a significance level of 0.01 was applied. SPSS Base for Windows v11.5 was used for all analyses.

Results

Patient Characteristics

Of the 68 patients who were included and randomly allocated to either treatment group, 65 (96%) completed the study. Discontinuation during the treatment phase occurred only in the placebo group and was due to refused treatment (n = 1), stroke (n = 1) and a partner who sustained an arm fracture (n = 1). An additional 3 cases were excluded from analysis because of missing data. Finally, 62 patients (91%) entered the analysis phase. An overview of the progress through the different phases of the trial is given in figure 1.

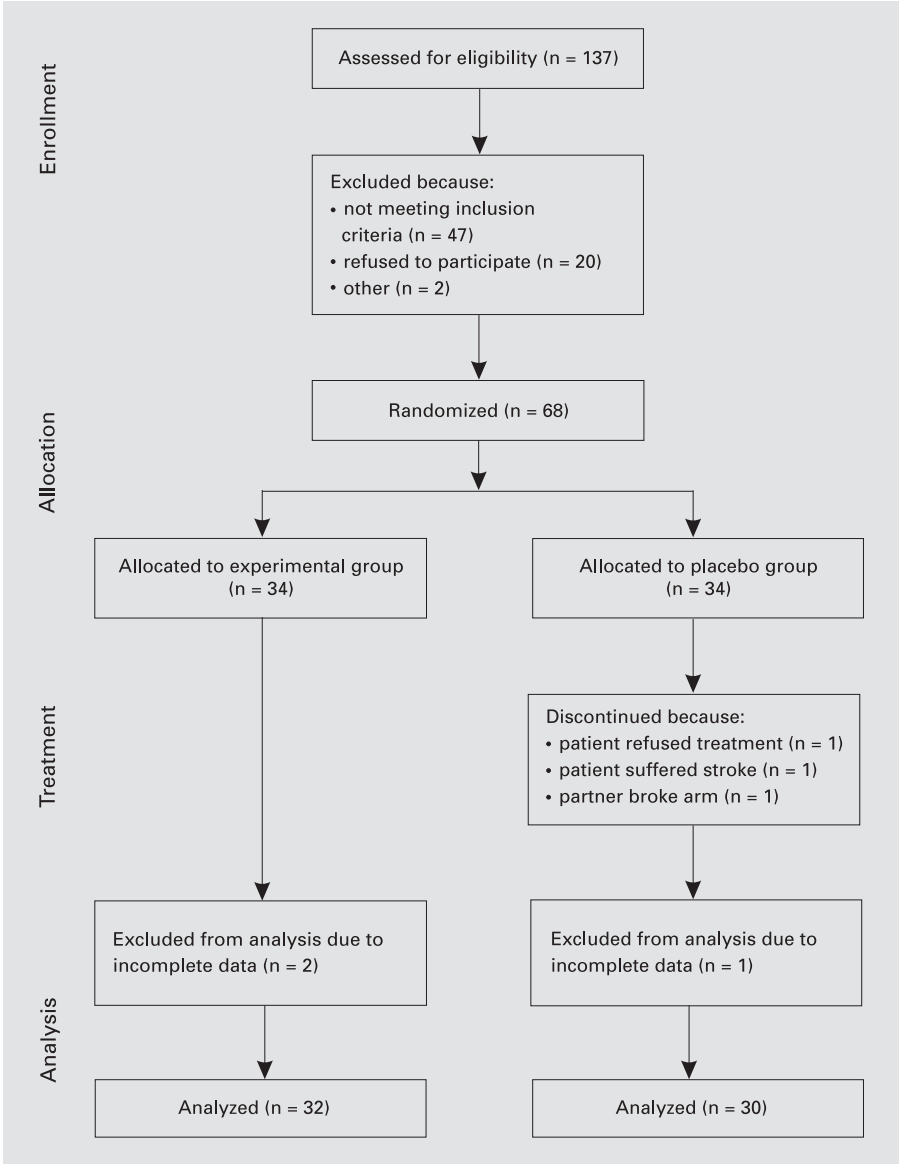

Fig. 1. Flow diagram of the progress through the phases of the trial.

Table 1. Patient characteristics

	Verum (n = 32)	Placebo (n = 30)	Total (n = 62)
Males/females	17/15	22/8	39/23
Age, years			
Mean (SD)	71.0 (7.8)	72.5 (8.2)	71.7 (8.0)
Range	52–87	55–87	52–87
Education, years			
Mean (SD)	10.3 (3.9)	10.7 (3.3)	10.5 (3.6)
Range	6–20	6–20	6–20
MMSE			
Mean (SD)	15.7 (6.8)	14.7 (7.2)	15.2 (6.9)
Range	0–26	1–26	0–26

The two treatment groups were not significantly different with regard to sex, age, education and MMSE (table 1). In total, there were 39 men and 23 women; their mean age was 71.7 years (SD 8.0; range 52–87). Mean years of education was 10.5 (SD 3.6; range 6–20) and mean MMSE score at baseline was 15.2 (SD 6.9; range 0–26). All patients lived with a partner/spouse or family member.

Treatment Effects

Cognitive Measures

Independent samples t tests indicated no significant differences between groups on cognitive measures before

Table 2. Means, standard deviations and repeated ANOVA of the cognitive measures before treatment (pre), after treatment (post) and after a treatment free period (delayed) of the verum and placebo groups

	Verum						Placebo						ANOVA					
	pre		post		delayed		pre		post		delayed		pre vs. post			pre vs. delayed		
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	F	d.f.	p	F	d.f.	p
Digit Span Forward	4.54	1.8	5.00	2.1	4.61	2.2	4.17	2.0	4.34	2.0	4.31	2.0	0.6	1, 55	0.45	0.0	1, 55	0.86
Digit Span Backward	3.25	1.9	3.36	1.7	3.29	1.8	3.41	2.2	3.28	1.8	3.14	1.9	0.5	1, 55	0.49	1.1	1, 55	0.30
Visual Memory Span Forward	3.89	1.7	3.79	2.1	4.18	2.1	4.28	2.1	4.00	2.2	3.90	2.5	0.3	1, 55	0.62	2.8	1, 55	0.10
Visual Memory Span Backward	3.21	2.8	3.36	2.1	2.93	2.1	3.00	2.2	3.24	2.4	3.38	2.4	0.1	1, 55	0.79	9.3	1, 55	0.10
Eight Words Test																		
Immediate Recall	15.43	6.6	15.00	8.1	16.11	7.4	13.00	8.1	13.62	8.1	14.17	9.0	1.2	1, 55	0.28	1.7	1, 55	0.69
Delayed Recall	0.89	1.6	0.71	1.3	1.11	1.8	0.41	1.0	0.76	1.3	0.76	1.7	3.6	1, 55	0.06	0.0	1, 55	0.77
Cued Recall	7.86	5.7	8.14	5.1	7.43	5.0	5.07	5.7	6.07	5.5	6.59	6.2	0.3	1, 55	0.57	2.4	1, 55	0.12
Face Recognition	5.14	5.2	6.36	3.0	6.71	3.9	6.14	4.1	6.21	3.8	7.31	3.3	0.9	1, 55	0.34	0.0	1, 55	0.83
Picture Recognition	14.21	6.2	13.39	5.8	11.71	8.6	12.00	7.6	12.14	7.5	12.00	7.3	0.0	1, 55	0.97	0.3	1, 55	0.58
Stroop Interference	31.10	17.0	32.70	17.1	30.50	16.2	26.65	14.5	30.29	15.7	28.10	13.7	0.2	1, 35	0.68	0.2	1, 36	0.64
Verbal Fluency Animals	10.00	6.9	9.39	6.1	8.82	7.1	7.72	6.2	7.83	6.1	7.69	6.8	1.1	1, 55	0.31	2.2	1, 55	0.14
Verbal Fluency Professions	6.79	5.3	7.46	5.5	6.64	5.9	4.79	4.2	5.24	5.2	4.79	4.6	1.1	1, 55	0.30	0.0	1, 55	0.96

Table 3. Means, standard deviations and repeated ANOVA of the behavioral measures before treatment (pre), after treatment (post) and after a treatment free period (delayed) of the verum and placebo groups

	Verum						Placebo						ANOVA					
	pre		post		delayed		pre		post		delayed		pre vs. post			pre vs. delayed		
	M	SD	M	SD	M	SD	M	SD	M	SD	M	SD	F	d.f.	p	F	d.f.	p
GDS-12R[a]	1.25	1.4	1.64	1.8	1.43	1.7	0.92	1.2	1.32	1.6	1.14	1.2	0.1	1, 54	0.92	0.6	1, 54	0.45
PGCMS[b]	13.32	2.9	13.04	3.7	13.04	3.5	14.21	3.3	14.50	3.8	14.39	3.4	0.7	1, 54	0.42	0.4	1, 54	0.42
PGCARS																		
Pleasure[b]	4.03	1.2	3.75	1.2	3.69	1.2	3.83	1.2	4.03	1.0	3.69	1.1	2.9	1, 59	0.09	0.4	1, 59	0.56
Anger[a]	1.97	1.2	1.72	1.1	1.84	1.0	1.90	1.2	1.90	1.0	2.00	1.1	1.7	1, 59	0.19	1.3	1, 59	0.27
Anxiety[a]	2.28	1.5	2.06	1.4	2.13	1.5	2.34	1.3	2.14	1.2	2.24	1.3	0.0	1, 59	0.98	0.0	1, 59	0.91
Sadness[a]	2.00	1.1	2.19	1.1	2.06	1.2	1.97	1.5	1.93	1.0	1.86	1.1	0.7	1, 59	0.39	0.4	1, 59	0.54
Interest[b]	3.59	1.3	3.69	1.3	3.34	1.4	3.10	1.3	3.83	1.3	3.66	1.3	4.4	1, 59	0.04	6.0	1, 59	0.02
Content[b]	4.19	0.8	4.03	0.9	3.94	0.8	4.17	0.9	4.48	0.7	4.24	0.9	3.7	1, 59	0.06	1.5	1, 59	0.23
GIP-28																		
Negative symptoms[a]	7.03	3.5	6.75	2.9	6.94	2.8	7.50	4.0	7.79	3.0	8.00	3.7	0.6	1, 59	0.44	0.5	1, 59	0.48
Cognitive symptoms[a]	12.75	5.2	10.37	4.3	10.97	5.6	12.66	5.6	9.93	6.1	12.00	6.3	0.2	1, 59	0.67	1.1	1, 59	0.31
Mood/affective symptoms[a]	5.69	5.1	3.44	4.9	3.78	5.3	5.10	5.3	3.41	4.1	3.52	4.4	1.2	1.59	0.28	1.1	1, 59	0.29
ADL[a]	7.38	6.6	7.78	6.5	8.00	6.7	8.21	6.8	8.52	7.8	10.03	9.2	2.1	1, 59	0.15	0.4	1, 59	0.56

[a] Low values are considered positive. [b] High values are considered positive.

treatment. Results of repeated measures ANOVAs suggested no significant differences on any of the cognitive measures between groups after treatment (table 2).

Self-Report Questionnaires Assessing Emotional Status

Groups did not differ on the GDS12R or PGCMS before the treatment period. Repeated measures ANOVAs revealed no significant differences between groups after treatment.

Informant-Based Ratings Assessing Functional and Emotional Status

Family caregivers of patients in the verum group and in the placebo group did not rate functional status on the ADL scale and emotional status on the PGCARS and GIP-28 differently. Repeated measures ANOVAs revealed no effects of the intervention on any of the functional and emotional measures based on the caregivers judgments (table 3).

Table 4. Means and standard deviations of scores on the applicability and efficacy questionnaire subscales of the verum and placebo groups

	Verum		Placebo		Total	
	M	SD	M	SD	M	SD
Part A (questions for the patient)						
Perceived burden	2.22	1.9	1.60	1.1	1.97	1.6
Perceived efficacy	1.10	1.4	0.77	1.3	0.97	1.3
Part B (questions for the family caregiver)						
Difficulties using the apparatus	1.54	1.3	1.70	1.6	1.61	1.4
Perceived burden for the family caregiver	1.22	1.3	1.26	1.4	1.24	1.3
Perceived burden for the patient	1.56	1.3	1.00	0.8	1.30	1.1
Perceived efficacy	1.13	1.3	1.26	1.2	1.19	1.2

Applicability and Efficacy of the Treatment

Questions for Patients

Patients from both the verum and the placebo group did not significantly differ on the subscales of the applicability and efficacy questionnaire. Thus, burden caused by the treatment and perceived efficacy of the treatment were not rated differently by the two groups (table 4).

The means (table 4) show that the burden and perceived efficacy was quite low in both groups.

Questions for Family Caregivers

Family caregivers who applied the real electrical stimulus also did not score differently on any of the subscales compared with those who applied sham stimulation.

Mean scores indicate hardly any difficulty using the apparatus, low burden and low perceived efficacy in both groups.

Discussion

Treatment Effects

We found that peripheral electrical nerve stimulation had no beneficial influence on the measures of cognitive and behavioral functioning in patients in the verum group compared with the placebo group after a treatment period of 6 weeks.

These results differ from the positive outcomes observed in previous studies using electrical stimulation in AD [12–17, 19], and the question rises how this discrepancy can be explained. Firstly, the number of participating patients here is 3 times the number included in the earlier studies. The lack of treatment effects in the present study could imply that the earlier findings observed in relatively small numbers of patients were not real treatment effects. Secondly, the present study included patients at all stages of AD, ranging from mild to severe, with a lower mean level of cognitive functioning than patients in previous studies using electrical stimulation. Le Bars et al. [40] observed a treatment effect of a ginko biloba extract on, among others, the cognitive subscale of the Alzheimer's Disease Assessment Scale, irrespective of the stage of dementia. However, an *improvement* was particularly observed in very mild to mild demented patients, whereas stabilization or hindering a further progression of the disease was characteristic for the more advanced stage of dementia. In other words, a treatment effect should not automatically be considered the same as an improvement in functioning. In addition, results from a recent review indicate that pharmacological treatment in AD stabilizes cognitive functioning and enhances ADL [41]. Thus, patient groups that are more homogenous with regard to disease severity may have generated different treatment effects than those reported here. A third difference between the current and former studies is the age of disease onset (it is earlier in the present study). There is ample evidence that early onset is associated with more severe cognitive impairment, more aggressive course of the disease, more AD pathology, greater neocortical cholinergic cell loss and a higher prevalence of apolipoprotein Eε4 [42, 43]. Therefore, the number of patients with early onset AD included in this study, may have reduced average treatment effects.

Taken together, the lack of treatment effects in the present study with a considerable number of patients may question the treatment effects observed in earlier studies

with fewer participants. However, patients' characteristics (level of cognitive functioning and age of onset of AD) differed between this study and previous studies. Perhaps the theory that stimulating the central nervous system improves metabolism and reactivates impaired neurons [5–7] does not hold for AD patients in a more advanced stage and/or patients with early onset AD. This suggestion is supported by Geddes and Cotman [44] who note that when neuropathology in AD is more severe, functional benefits of plasticity become less certain.

A large replication study with AD patients in an earlier phase of the disease might provide a more definitive conclusion about the beneficial effect of peripheral electrical nerve stimulation in AD.

Treatment Applicability

We also examined how the patients underwent the treatment and how the family caregiver experienced applying the treatment. Interestingly, the majority of the patients and the caregivers were very positive about the procedure, and applying the daily treatment was accompanied with minimal burden.

Several studies have focused on the effects of providing care to a demented relative and found an increased strain on psychological and physical health of the family caregiver [45, 46]. Other studies report a positive gain from caregiving [47, 48] or captured the caregivers' experience in the term vigilance; operationalized as 'supervising' and 'being there' [49]. Another group found that when caregivers provided end-of-life care at home they showed faster recovery from depression and psychological stress after death of their relatives than caregivers of patients who were institutionalized [50]. Also, a study on nursing-home placement of cognitively impaired elderly who were cared for by their relatives, found that caregivers expressed a higher preference for institutionalization if he or she experienced less caregiving satisfaction [51]. In sum, the present study is, to our knowledge, the first to show that an active role for the family caregiver is feasible in symptomatic treatment of a demented relative.

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References

1 Francis PT, Palmer AM, Snape M, Wilcock GK: The cholinergic hypothesis of Alzheimer's disease: A review of progress. J Neurol Neurosurg Psychiatry 1999;66:137–147.

2 Mann DM, Yates PO, Marcyniuk B: Alzheimer's presenile dementia, senile dementia of Alzheimer type and Down's syndrome in middle age form an age related continuum of pathological changes. Neuropathol Appl Neurobiol 1984;10:185–207.

3 Whitehouse PJ, Price DL, Struble RG, Clark AW, Coyle JT, Delon MR: Alzheimer's disease and senile dementia: Loss of neurons in the basal forebrain. Science 1982;215:1237–1239.

4 Vogels OJM, Broere CA, ter Laak HJ, ten Donkelaar HJ, Nieuwenhuys R, Schulte BP: Cell loss and shrinkage in the nucleus basalis Meynert complex in Alzheimer's disease. Neurobiol Aging 1990;11:3–13.

5 Swaab DF: Brain aging and Alzheimer's disease, 'wear and tear' versus 'use it or lose it'. Neurobiol Aging 1991;12:317–324.

6 Swaab DF, Dubelaar EJG, Hofman MA, Scherder EJA, Van Someren EJW, Verwer RWH: Brain aging and Alzheimer's disease; use it or lose it. Prog Brain Res 2002;138:343–373.

7 Swaab DF, Dubelaar EJG, Scherder EJA, Van Someren EJW, Verwer RWH: Therapeutic strategies for Alzheimer disease: Focus on neuronal reactivation of metabolically impaired neurons. Alzheimer Dis Assoc Disord 2003;17(suppl 4):S114–S122.

8 Kobayashi S, Ohashi Y, Ando S: Effects of enriched environments with different durations and starting times on learning capacity during aging in rats assessed by a refined procedure of the Hebb-Williams maze task. J Neurosci Res 2002;70:340–346.

9 Luijpen MW, Scherder EJA, Van Someren EJW, Swaab DF, Sergeant JA: Non-pharmacological interventions in cognitively impaired and demented patients – a comparison with cholinesterase inhibitors. Rev Neurosci 2003;14:343–368.

10 Nakajima K, Uchida S, Suzuki A, Hotta H, Aikawa Y: The effect of walking on regional blood flow and acetylcholine in the hippocampus in conscious rats. Auton Neurosci 2003;103:83–92.

11 Dutar P, Lamour Y, Jobert A: Activation of identified septo-hippocampal neurons by noxious peripheral stimulation. Brain Res 1985;328:15–21.

12 Scherder EJA, Bouma A, Steen AM: Influence of transcutaneous electrical nerve stimulation on memory in patients with dementia of the Alzheimer type. J Clin Exp Neuropsychol 1992;14:951–960.

13 Scherder EJA, Bouma A, Steen AM: Effects of short-term transcutaneous electrical nerve stimulation on memory and affective behaviour in patients with probable Alzheimer's disease. Behav Brain Res 1995;67:211–219.

14 Scherder EJA, Bouma A, Steen LM: Effects of 'isolated' transcutaneous electrical nerve stimulation on memory and affective behavior in patients with probable Alzheimer's disease. Biol Psychiatry 1998;43:417–424.

15 Scherder EJA, Van Someren EJW, Swaab DF: Transcutaneous electrical nerve stimulation (TENS) improves the rest-activity rhythm in midstage Alzheimer's disease. Behav Brain Res 1999;101:105–107.

16 Scherder EJA, Bouma A: Effects of transcutaneous electrical nerve stimulation on memory and behavior in Alzheimer's disease may be stage-dependent. Biol Psychiatry 1999;45:743–749.

17 Van Someren EJW, Scherder EJA, Swaab DF: Transcutaneous electrical nerve stimulation (TENS) improves circadian rhythm disturbances in Alzheimer disease. Alzheimer Dis Assoc Disord 1998;12:114–118.
18 Van Dijk KRA, Scherder EJA, Scheltens P, Sergeant JA: Effects of transcutaneous electrical nerve stimulation (TENS) on non-pain related cognitive and behavioural functioning. Rev Neurosci 2002;13:257–270.
19 Guo Y, Shi X, Uchiyama H, Hasegawa A, Nakagawa Y, Tanaka M, et al: A study on the rehabilitation of cognitive function and short-term memory in patients with Alzheimer's disease using transcutaneous electrical nerve stimulation. Front Med Biol Eng 2002;11: 237–247.
20 Tales A, Troscianko T, Lush D, Haworth J, Wilcock GK, Butler SR: The pupillary light reflex in aging and Alzheimer's disease. Aging (Milano) 2001;13:473–478.
21 McKhann G, Drachman D, Folstein M, Katzman R, Price D, Stadlan EM: Clinical diagnosis of Alzheimer's disease: Report of the NINCDS-ADRDA Work Group under the auspices of Department of Health and Human Services Task Force on Alzheimer's Disease. Neurology 1984;34:939–944.
22 Folstein MF, Folstein SE, McHugh PR: 'Mini-mental state'. A practical method for grading the cognitive state of patients for the clinician. J Psychiatr Res 1975;12:189–198.
23 Rasmussen MJ, Hayes DL, Vlietstra RE, Thorsteinsson G: Can transcutaneous electrical nerve stimulation be safely used in patients with permanent cardiac pacemakers? Mayo Clin Proc 1988;63:443–445.
24 Wechsler D: A standardized memory test for clinical use. J Psychol 1945;19:87–95.
25 Lindeboom J, Jonker C: Amsterdamse Dementie-Screeningstest (ADS-6) Handleiding. Lisse, Swets & Zeitlinger, 1989.
26 Wilson MA, Cockburn J, Baddely A: The Rivermead Behavioural Memory Test. Reading, Thames Valley Test Co., 1985.
27 Stroop JP: Studies of interference in serial verbal reactions. J Exp Psychol 1935;18:646–662.
28 Benton AL, Hamster KS: Multilingual aphasia examination, revised. Iowa City, University of Iowa, 1978.
29 Yesavage JA, Brink TL, Rose TL, Lum O, Huang V, Adey M, et al: Development and validation of a geriatric depression screening scale; a preliminary report. J Psychiatr Res 1983;17:37–49.
30 Burke WJ, Houston MJ, Boust SJ, Roccaforte WH: Use of the geriatric depression scale in dementia of the Alzheimer type. J Am Geriatr Soc 1989;37:856–860.
31 Sutcliffe C, Cordingley L, Burns A, Mozley CG, Bagley H, Huxley P, et al: A new version of the geriatric depression scale for nursing and residential home populations: The geriatric depression scale (residential) (GDS-12R). Int Psychogeriatr 2000;12:173–181.
32 Lawton MP: The Philadelphia Geriatric Center Morale Scale: A revision. J Gerontol 1975; 30:85–89.
33 Lawton MP, Van Haitsma K, Klapper J: Observed affect in nursing home residents with Alzheimer's disease. J Gerontol B Psychol Sci Soc Sci 1996;51:3–14.
34 De Jonghe JFM, Ooms ME, Ribbe MW: Short version of the Dutch Behavioral Rating Scale for Psychogeriatric Inpatients (GIP-28) (in Dutch). Tijdschr Gerontol Geriatr 1997;28: 119–123.
35 Verstraten PFJ, Van Eekelen CWJM: Handleiding voor de GIP: Gedragsobervatieschaal voor de intramurale psychogeriatrie. Deventer, Van Loghum Slaterus, 1987.
36 Linn MW: Physical and Mental Impairment-of-Function Evaluation (PAMIE). Psychopharmacol Bull 1988;24:755–757.
37 De Jonghe JFM, Goedhart AW, Ooms ME, Kat MG, Kalisvaart KJ, van Ewijk WM, et al: Negative symptoms in Alzheimer's disease: a confirmatory factor analysis. Int J Geriatr Psychiatry 2003;18:748–753.
38 Katz S, Ford AB, Moskowitz RW, Jackson BA, Jaffe MW: Studies of illness in the aged – the index of ADL – a standardized measure of biological and psychosocial function. JAMA 1963;185:914–919.
39 Holmes D, Teresi J, Weiner A, Monaco C, Ronch J, Vickers R: Impacts associated with special care units in long-term care facilities. Gerontologist 1990;30:178–183.
40 Le Bars PL, Velasco FM, Ferguson JM, Dessain EC, Kieser M, Hoerr R: Influence of the severity of cognitive impairment on the effect of the *Ginkgo biloba* extract EGb 761 in Alzheimer's disease. Neuropsychobiology 2002; 45:19–26.
41 Standridge JB: Pharmacotherapeutic approaches to the treatment of Alzheimer's disease. Clin Ther 2004;26:615–630.
42 Cedazo-Minguez A, Cowburn RF: Apolipoprotein E: A major piece in the Alzheimer's disease puzzle. J Cell Mol Med 2001;5:254–266.
43 Ho GJ, Hansen LA, Alford MF, Foster K, Salmon DP, Galasko D, et al: Age at onset is associated with disease severity in Lewy body variant and Alzheimer's disease. Neuroreport 2002;13:1825–1828.
44 Geddes JW, Cotman CW: Plasticity in Alzheimer's disease: Too much or not enough? Neurobiol Aging 1991;12:330–333.
45 Sadik K, Wilcock G: The increasing burden of Alzheimer disease. Alzheimer Dis Assoc Disord 2003;17(suppl 3):S75-S79.
46 Pinquart M, Sorensen S: Differences between caregivers and noncaregivers in psychological health and physical health: a meta-analysis. Psychol Aging 2003;18:250–267.
47 Kramer BJ: Gain in the caregiving experience: Where are we? What next? Gerontologist 1997; 37:218–232.
48 Schulz R, Newsom J, Mittelmark M, Burton L, Hirsch C, Jackson S: Health effects of caregiving: The caregiver health effects study: An ancillary study of the Cardiovascular Health Study. Ann Behav Med 1997;19:110–116.
49 Mahoney DF: Vigilance. Evolution and definition for caregivers of family members with Alzheimer's disease. J Gerontol Nurs 2003;29: 24–30.
50 Schulz R, Mendelsohn AB, Haley WE, Mahoney D, Allen RS, Zhang S, et al: End-of-life care and the effects of bereavement on family caregivers of persons with dementia. N Engl J Med 2003;349:1936–1942.
51 Spruytte N, Van Audenhove C, Lammertyn F: Predictors of institutionalization of cognitively-impaired elderly cared for by their relatives. Int J Geriatr Psychiatry 2001;16:1119–1128.